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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/026,586	12/18/2001	Manoj Kumar	GC558D1	9370

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GENENCOR INTERNATIONAL, INC.
ATTENTION: LEGAL DEPARTMENT
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EXAMINER

RAO, MANJUNATH N

ART UNIT PAPER NUMBER

1652

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/026,586

Applicant(s)

KUMAR, MANOJ

Examiner

Manjunath N. Rao, Ph.D.

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A. SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 August 2002.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 20-31 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 20-31 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 18 December 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 6) ☐ Other:

DETAILED ACTION

Claims 20-31 are still at issue and are present for examination.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Claim Objections

Claims 20, 24, and 30 are objected to because of the following informalities: Claims 20, 24, 30 use abbreviations for some enzyme activities without any expansion when they are recited for the first time. Appropriate correction is required.

Claims 27-31 are objected to because of the following informalities: Biological names in claims 27-31 are not recited in italics. Appropriate correction is required.

Claim 31 is objected to because of the following informality: The claim does not refer to the group of enzyme activities in the alternative as required by the preceding phrase. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Art Unit: 1652

Claims 21, 23 and claims 22, 24 which depend from claims 21 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 21 and 23 recite the phrase "enzyme is a dehydrogenase activity" and "enzyme is a reductase activity" respectively. It is not clear to the Examiner as to what applicants mean by the above phrase. It appears that applicants intended to recite "enzyme has dehydrogenase activity" or "enzyme has reductase activity" judging from the recitations in the dependent claims. If this is so amending the claims accordingly would overcome this rejection.

Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 22 recites the phrase "wherein said dehydrogenase activity includes". The metes and bounds of the word "includes" in the context of the above claim is not clear to the Examiner.

Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 24 recites the phrase "wherein said reductase activity includes". The metes and bounds of the word "includes" in the context of the above claim is not clear to the Examiner.

Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 27 recites the phrase "wherein the yeast includes *Candida* and

Art Unit: 1652

Cryptococcus". The metes and bounds of the word "includes" in the context of the above claim is not clear to the Examiner.

Claims 30 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim s 30 and 31 recites the limitation "and said carbon source comprises" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made:

Claims 20-30, are rejected under 35 U.S.C. 103(a) as being unpatentable over Murakawa et al. (Agric. Biol. Chem., Vol 41(9):1799-1800), Hardy et al. (US 4,945, 052 issued Jul 31, 1990) and Anderson et al. (US 5,032,514, 7-16-1991). Claims 20-31 in this instant application are drawn to a recombinant yeast capable of utilizing keto-L-gulonic acid to produce ascorbic acid or an ascorbic acid stereoisomer comprising or expressing a heterologous gene for an oxidative and reductive enzyme such as 2-keto-D-gluconic acid dehydrogenase and 2,5 DGK reductase respectively, rendering the yeast capable of utilizing 2-keto-L-gulonic acid (2-KLG), an intermediate in the biosynthesis of ascorbic acid and finally bioconverting KLG to ascorbic acid, wherein said yeast is a member of Cryptococcaceae, belonging to genus *Candida* or *Cryptococcus* specifically *C.blankii* or *C.dimennae*.

Art Unit: 1652

Murakawa et al. teach the production of ascorbic acid from non-recombinant yeasts using wide variety of sugars including glucose. However, the yields appear to be low. Thus, it appears that it was well known in the art that 2,3-DKG occurs among yeasts and that they are capable of producing ascorbic acid. Andersen et al. teach a metabolic pathway for engineering an increased production of ascorbic acid intermediates by using recombinant technology by transfer of genes responsible for the bioconversion of a six carbon sugar such as glucose to 2-KLG which is next oxidized to ascorbic acid using the very same enzymes taught in this instant application. (See entire document, specifically, column 1, lines 55-69 and column 2, lines 61-66; column 3 lines 33-36, 43-48, 63-69; column 4, lines 26-32, 43-60; column 5 line 43; column 11, lines 15-43, column 13, lines 26-36, 37-65, column 18-19, example 4). However, the reference does not teach the utilization of yeasts for the fermentative method or the bioconversion method. The reference does teach that the recombinant technique can be used using any appropriate host cells (see column 7, lines 63-68 and column 8, lines 1-8). Hardy et al. teach the production of vitamin C precursor, 2, 5-DKG, in genetically modified microorganisms including several bacteria, fungi and yeasts (see column 5, last para) by transforming yeast host cells using a vector expressing the enzyme required for converting 2,5DKG to 2-KLG. The reference teaches recombinant methods and suggests the use of a list of microorganisms and mammalian cells as host cells.

With the above references in hand, it would have been obvious to one skilled in the art at the time the invention was made to combine the teachings of Murakawa et al. with that of Andersen et al. or Hardy et al. to engineer a yeast cell such as a *Candida*, capable of utilizing 2KLG and convert it into ascorbic acid. Murakawa et al. teach that yeasts are capable of producing ascorbic acid. Hardy et al. teach the use of yeasts as host organisms. Because the production of ascorbic acid is low among yeasts, one skilled in the art would be motivated to combine the teachings of Murakawa et al. with that of the molecular biological techniques of

Art Unit: 1652

Andersen et al. to develop yeasts capable of utilizing glucose more efficiently and produce ascorbic acid in large amounts such that ascorbic acid can be produced on a commercial scale in a one pot synthesis. Furthermore, Andersen et al. reference also teach that one would be motivated to do this as they are several advantages of having a yeast; a well known industrial microorganism, capable of producing vitamin C, to produce large amounts of ascorbic acid which has a huge demand in food and pharmaceutical industry. One would have a reasonable expectation of success since Murakawa et al. demonstrate the production of vitamin C from yeasts which are well known as fermentation work horse and Andersen et al. provide the entire metabolic machinery and the genes and enzymes necessary for doing the same and Hardy et al. demonstrate that yeasts can be used as host cells to introduce vectors for vitamin C precursor enzymes.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art to have performed the claimed invention.

Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Murakawa et al. (Agric. Biol. Chem., Vol 41(9):1799-1800), Hardy et al. (US 4,945, 052 issued Jul 31, 1990) and Anderson et al. (US 5,032,514, 7-16-1991) as applied to claims 20-30 above, and further in view of Saito et al. (Appl. Environ. Microbiol., 1997, Vol. 63(2):454-460). Claim 31 is drawn to a recombinant yeast capable of utilizing keto-L-gulonic acid to produce ascorbic acid or an ascorbic acid stereoisomer comprising using L-sorbitol by expressing a heterologous gene for an oxidative and reductive enzyme such as L-sorbose dehydrogenase, to produce KLG from sorbitol.

The references of Murakawa et al., Hardy et al. and Anderson et al. have all been discussed above. Saito et al. disclose the cloning of the genes coding for L-sorbose

Art Unit: 1652

dehydrogenase and also teach the use of a recombinant bacteria transformed with said gene capable of using sorbitol for production of KLG. However, the reference does not teach a recombinant yeast strain comprising the said genes.

Combining the above references it would have been obvious to one of ordinary skill in the art to transform a yeast cell with the sorbitol dehydrogenase activity taught by Saito et al. in order to obtain a recombinant yeast capable of using sorbitol to produce KLG and further convert the same to ascorbic acid. One of ordinary skill in the art would have been motivated to do so in order to use a cheap carbon source, the sorbitol for production of ascorbic acid. One of ordinary skill in the art would have a reasonable expectation of success since all the references except for Saito et al. teach the making of a yeast or a recombinant yeast for ascorbic acid production and Saito et al. specifically teach the use of sorbitol dehydrogenase genes for achieving the same goal using a cheap carbon source.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art to have performed the claimed invention.


This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Art Unit: 1652

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


MANJUNATH RAO
PATENT EXAMINER

Manjunath N. Rao
6/13/03